Stavudine

Brand Name: Zerit
Drug Class: Nucleoside Reverse Transcriptase Inhibitors

Drug Description

Stavudine, a synthetic antiretroviral agent, is a dideoxynucleoside reverse transcriptase inhibitor. It is an analogue of thymidine, a naturally occurring pyrimidine nucleoside. It differs from thymidine in the 2'-3' double bond on the deoxyribose moiety and the replacement of the 3'-hydroxyl group with hydrogen. The absence of a free 3'-hydroxyl group results in the inability of stavudine to form phosphodiester linkages at this position. [1]

HIV/AIDS-Related Uses

Stavudine was approved by the FDA on June 24, 1994, for use in combination with other antiretroviral agents and is indicated for the treatment of HIV-1 infection in adults and pediatric patients.[2] [3] Additionally, stavudine is indicated for the treatment of patients with HIV infection who have received prolonged previous treatment with zidovudine. The duration of clinical benefit from antiretroviral therapy involving stavudine may be limited. If disease progression occurs during stavudine treatment, an alternative antiretroviral therapy is recommended.[4]

While stavudine was used as monotherapy in initial studies evaluating the safety and efficacy of the drug, it should not be used alone in the management of HIV infection. Stavudine is also used in conjunction with other antiretroviral agents for postexposure prophylaxis in health care workers and other individuals exposed occupationally to blood, tissues, or other body fluids associated with a risk for transmission of the HIV virus.[5]

Pharmacology

Stavudine is phosphorylated by cellular kinases to the active metabolite stavudine triphosphate. Stavudine triphosphate inhibits HIV replication by two known mechanisms. It inhibits HIV reverse transcriptase (RT) by competing with the natural substrate deoxythymidine triphosphate. Its incorporation into viral DNA causes termination of DNA chain elongation because stavudine lacks the essential 3'-OH group. Stavudine triphosphate inhibits cellular DNA polymerase beta and gamma, and markedly reduces the synthesis of mitochondrial DNA.[6] The stavudine concentration ranging from 0.009 to 4 micromolar is required to inhibit HIV replication by 50% in vitro. The in vitro potency of stavudine against HIV is similar to that of zidovudine.[7]

Following oral administration to HIV-infected patients, stavudine is rapidly absorbed, with peak plasma concentrations occurring within 1 hour after dosing. The systemic exposure to stavudine is the same following administration as capsules or solution.[8] Stavudine has an oral bioavailability of 68.2% to 104.6% in adults and 44.2% to 108.6% in children. Stavudine may be taken with or without food; administration with food results in a decrease in maximum plasma concentration (Cmax) of approximately 45%. However, the systemic availability, as measured by the area under the plasma concentration/time curve (AUC), remains unchanged.[9] Data from single- and multiple-dosing studies indicate that peak plasma concentrations and AUC of stavudine increase in proportion to dose over the dosage range of 0.03 to 4 mg/kg; there is no evidence that accumulation occurs following multiple doses.[10]

Stavudine distributes equally between red blood cells and plasma. In a study of 8 children, stavudine crossed the blood brain barrier and distributed into the cerebrospinal fluid (CSF) with a mean CSF to plasma concentration of 59%.[11] Stavudine is distributed into CSF following oral administration. In a limited number of HIV infected adults receiving oral stavudine in a dosage of 40 mg twice daily in conjunction with other antiretroviral agents, CSF concentrations of the drug averaged 71 ng/ml in samples taken 1 hour after a dose at 8 weeks of therapy; steady-state peak plasma concentrations at this time averaged 930 ng/ml. Similar CSF and plasma concentrations of stavudine were measured in these patients after almost 2 years of continuous therapy. Following a single intravenous dose in HIV infected individuals, the volume of distribution is 46 l in adults and 0.73 l/kg in pediatric patients 5 weeks to 15 years of age. Results of a study in HIV infected men indicate that stavudine is distributed into semen in concentrations approximating those of

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Pharmacology (cont.)

concurrent plasma concentrations.[12]

Stavudine is in FDA Pregnancy Category C.[13] Adequate and well-controlled studies have not been done in pregnant women. It is not known whether stavudine crosses the placenta in humans; however, it does cross the placenta in rats. It is not known whether stavudine reduces perinatal transmission of HIV infection as does zidovudine. Stavudine should be used with caution during pregnancy and only if clearly needed. No evidence of impaired fertility was seen in rats given stavudine at doses that resulted in peak serum concentrations that were 216 times those observed in humans who received a clinical dosage of 1 mg/kg per day. Rats and rabbits exposed to levels of stavudine up to 399 and 183 times, respectively, the clinical dosage for humans revealed no evidence of teratogenicity. The incidence of common skeletal variation, incomplete ossification, and neonatal mortality increased in rats exposed to 399 times the human exposure. A slight postimplantation loss was seen at 216 times the human exposure. To monitor maternal-fetal outcomes of pregnant women exposed to antiretroviral medications, including stavudine, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263 or online at http://www.APRegistry.com.[14]

It is not known whether stavudine is distributed into human milk; however, it is distributed into milk in rats. Because of the potential for HIV transmission and for potential adverse effects in breast-fed infants, mothers receiving antiretroviral medications should be instructed not to breastfeed.[15]

Binding of stavudine to serum proteins is negligible. The half-life of stavudine in the presence of normal renal function is 1.14 to 1.74 hours in adults and 0.7 to 1.22 hours in children. In patients with renal function impairment (creatinine clearances of less than 25 ml/min), the half-life is approximately 3.7 to 5.5 hours. The time to peak concentration is 0.5 to 1.5 hours. The intracellular half-life of stavudine triphosphate is approximately 3.5 hours, with peak serum concentration of approximately 1.4 mcg/ml after a single oral dose of 70 mg stavudine.[16]

Renal elimination accounts for about 40% of overall clearance into urine over a 6 to 24 hour period, regardless of the route of administration.[17] Approximately 50% of an administered dose undergoes nonrenal elimination. Although the exact metabolic fate is unknown, stavudine may be cleaved to thymine, and the subsequent degradation or utilization of thymine may account for the unrecovered stavudine. It is not known whether stavudine is removed by peritoneal dialysis.[18] The mean renal clearance is about twice the average endogenous creatinine clearance, indicating active tubular secretion in addition to glomerular filtration. Oral clearance of stavudine decreases and the terminal elimination half-life increases as creatinine clearance decreases; therefore, dosage of stavudine should be modified in patients with reduced creatinine clearance and in patients receiving maintenance hemodialysis.[19]

HIV-1 isolates with reduced susceptibility to stavudine have been selected in vitro and were also obtained from patients treated with stavudine. Phenotypic analysis of HIV-1 isolates from 61 stavudine-treated patients receiving prolonged six to 29 months of stavudine monotherapy showed that post-therapy isolates from 4 patients exhibited IC50 values more than fourfold (ranging from seven- to 16-fold) higher than the average pretreatment susceptibility of baseline isolates. Of these, HIV-1 isolates from one patient contained the zidovudine-resistance-associated mutations T215Y and K219E, and isolates from another patient contained the multiple-nucleoside-resistance-associated mutation Q151M. Mutations in the RT gene of HIV-1 isolates from the other two patients were not detected. The genetic basis for stavudine susceptibility changes has not been identified.[20]

Adverse Events/Toxicity

Common adverse effects seen with the use of stavudine include peripheral neuropathy, arthralgia, hypersensitivity, myalgia, anorexia, chills and fever, rash, asthenia, gastrointestinal disturbances, headache, insomnia, and fat redistribution.[21]

Studies suggest that lactic acidosis and severe

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Adverse Events/Toxicity (cont.)

hepatomegaly with steatosis may be more often associated with antiretroviral regimens containing stavudine. Female gender, obesity, and prolonged nucleoside exposure may be risk factors; however, fatal lactic acidosis has been reported in patients with and without known risk factors for liver disease. Generalized fatigue, digestive symptoms (nausea, vomiting, abdominal pain, and sudden unexplained weight loss); respiratory symptoms (tachypnea, dyspnea); or neurologic symptoms such as motor weakness might be indicative of lactic acidosis. Therapy with stavudine should be suspended in patients with suspected lactic acidosis. Permanent discontinuation of stavudine should be considered in patients with confirmed lactic acidosis.[22]

An increased risk of hepatotoxicity, which may be fatal, may occur in patients treated with stavudine in combination with didanosine and hydroxyurea. Fatal and nonfatal pancreatitis has occurred when stavudine was part of a combination regimen that included didanosine with or without hydroxyurea. Treatment should be suspended in patients with suspected pancreatitis. Reinstitution of stavudine after a confirmed diagnosis of pancreatitis should be undertaken with caution. The new regimen should not include either didanosine or hydroxyurea. Fatal lactic acidosis has occurred in pregnant women who received the combination of stavudine and didanosine with other antiretroviral agents. It is unclear if pregnancy augments the risk of lactic acidosis/hepatic steatosis syndrome reported in nonpregnant individuals receiving nucleoside analogues.[23]

Motor weakness has been reported rarely in patients receiving combination antiretroviral therapy including stavudine. Most of these cases have occurred in the setting of lactic acidosis. If motor weakness develops, stavudine therapy should be discontinued. Peripheral neuropathy, manifested by numbness, tingling, or pain in the hands or feet, has been reported in patients receiving stavudine. Peripheral neuropathy has occurred more frequently in patients with advanced HIV disease, a history of neuropathy, or concurrent neurotoxic drug therapy, including didanosine. Treatment with stavudine should be interrupted if symptoms of peripheral neuropathy occur. Stavudine-induced neuropathy may resolve completely if stavudine is withdrawn promptly; however, in some cases symptoms may worsen temporarily upon withdrawal. If symptoms resolve completely, patients may tolerate resumption of stavudine treatment at a lowered dose. If peripheral neuropathy recurs after resumption, permanent discontinuation of stavudine should be considered.[24]

Drug and Food Interactions

Caution should be used in coadministration of stavudine with other drugs that may cause peripheral neuropathy, such as chloramphenicol, cisplatin, dapsone, didanosine, ethambutol, ethionamide, hydralazine, isoniazid, lithium, metronidazole, nitrofurantoin, phenytoin, vincristine, and zalcitabine. Didanosine or hydroxyurea may increase the risk of potentially fatal hepatotoxicity or pancreatitis if taken concurrently with stavudine.[25]

Concomitant use of stavudine and zidovudine is not recommended due to possible competitive inhibition of the intracellular phosphorylation of stavudine. In vitro studies detected an antagonistic antiviral effect between stavudine and zidovudine at a molar ratio of 20 to 1, respectively; concurrent use is not recommended until in vivo studies demonstrate that these medications are not antagonistic in their anti-HIV activity.[26]

Contraindications

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including stavudine and other antiretrovirals. Fatal lactic acidosis has been reported in pregnant women who received the combination of stavudine and didanosine with other antiretroviral agents. The combination of stavudine and didanosine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risks. Fatal and nonfatal pancreatitis has occurred during therapy when stavudine was part of a combination regimen that included didanosine, with or without

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Contraindications (cont.)

hydroxyurea, in both treatment-naive and treatment-experienced patients, regardless of degree of immunosuppression.[27]

Stavudine is contraindicated in patients with clinically significant hypersensitivity to stavudine or to any of the components contained in the formulation.[28]

Risk-benefit should be considered in patients with alcoholism, hepatic function impairment, peripheral neuropathy, or renal function impairment.[29]

Clinical Trials

For information on clinical trials that involve Stavudine, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Stavudine AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[30]

Dosage Form: Immediate release (IR) capsules containing 15, 20, 30, or 40 mg stavudine.

Oral solution containing 1 mg/ml stavudine.[31]

Extended-release (XR) capsules containing 37.5, 50, 75, or 100 mg stavudine.[32]

The recommended dose based on body weight is as follows: 40 mg twice daily for patients weighing 60 kg (132 lbs) or more and 30 mg twice daily for patients weighing less than 60 kg (132 lbs). The interval between doses of stavudine should be 12 hours. The recommended dose for pediatric patients at least 14 days old and weighing less than 30 kg (66 lbs) is 1 mg/kg/dose, given every 12 hours. Pediatric patients weighing 30 kg (66 lbs) or greater should receive the recommended adult dosage.[33]

Dosing should be adjusted in patients with impaired renal function according to the recommendations in the manufacturer's prescribing information. For patients on hemodialysis, the recommended dose is 20 mg every 24 hours (patients weighing more than 60 kg) or 15 mg every 24 hours (patients weighing less than 60 kg).[34]

Storage: Store stavudine immediate release capsules and powder for reconstitution in tightly closed containers at room temperature, 15 C to 30 C (59 F to 86 F). Protect powder from excessive moisture. Refrigerate reconstituted solution at 2 C to 8 C (36 F to 46 F) and discard unused solution after 30 days.[35] Store stavudine extended release capsules in tightly closed containers at 25 C (77 F).[36]

Chemistry

CAS Name: Thymidine, 2',3'-didehydro-3'-deoxy-[37]

CAS Number: 3056-17-5[38]

Molecular formula: C10-H12-N2-O4[39]

C53.57%, H5.39%, N12.49%, O28.54%[40]

Molecular weight: 224.22[41]

Melting point: 165 C to 166 C (Horwitz); 174 C (Beach)[42]

Physical Description: White to off-white crystalline solid.[43]

Stability: Oral solution should be discarded 30 days after reconstitution.[44]

Solubility: About 83 mg/ml in water and 30 mg/ml in propylene glycol at 23 C. The n-octanol/water partition coefficient of stavudine at 23 C is 0.144.[45]

Other Names

BMY-27857[46]

d4T[47]

Estavudina[48]

Further Reading

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Further Reading (cont.)

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Manufacturer Information

Stavudine
Bristol - Myers Squibb Co
PO Box 4500
Princeton, NJ 08543-4500
(800) 321-1335

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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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